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Melatonin in the treatment of fibromyalgia symptoms: A systematic review

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ABSTRACT

The available pharmacological modalities for the treatment of fibromyalgia (FM) are associated with a variety of adverse effects and limited benefits. In this study, we systematically reviewed the impact of melatonin in the treatment of FM. Interventional studies, either controlled or uncontrolled and randomized or non-randomized, were included. PubMed, EMBASE, Scopus, Web of Science, and the Cochrane Library were searched without time limitation. Primary outcome measures were the effect of melatonin on the disease impact, pain, sleep quality, tender point count, fatigue, anxiety, stiffness, and depression in FM patients. Four studies, reporting the effect of melatonin on 98 patients, were eligible to include. All the studies reported the positive effect of melatonin on the FM symptoms. No major adverse event was reported. A significant level of heterogeneity was observed between the studies. Therefore, further high-quality controlled clinical trials are needed to understand the role of melatonin in FM treatment fully.

1. Introduction

Melatonin is an essential hormone of the pineal gland with pleiotropic activity. Many extra-pineal organs have also been identified as the melatonin producers, such as skeletal muscles, gastrointestinal tract, immune system cells, liver, spleen, kidney, retina, and heart [1,2]. A wide range of physiological and metabolic functions have been reported for melatonin. In addition to the analgesic, antioxidant, and anti-inflammatory effects, melatonin regulates the circadian biology, cellular autophagy, immune system, body temperature, and reproduction [3]. The role of melatonin in a variety of human diseases such as cancers, mental disorders, cardiovascular disorders, intestinal disorders, retinal disorders, renal disorders, musculoskeletal disorders, and metabolic disorders has been demonstrated [4–7]. Melatonin also has a protective effect against obesity, diabetes, sepsis, and fibrosis, and significantly improves sleep quality, fatigue, anxiety, and depression [5,8,9]. An anti-nociceptive role has proposed for melatonin as well, although still controversial [10]. Considering the versatile and multifunctional effects of melatonin and its role in different clinical conditions, it has been described as the "miracle far beyond the pineal gland" [11].

Fibromyalgia (FM) is one of the most prevalent debilitating conditions characterized by chronic and widespread pain, tenderness, and functional symptoms [12–14]. The global prevalence of FM is estimated to be 2.7%, ranging from 0.4% in Greece [15] to 9.3% in Tunisia [16]. The mean prevalence is estimated by 3.1% in the Americas, 2.5% in Europe, and 1.7% in Asia [17]. FM is associated with sleep disorders, fatigue, anxiety, and depression [18]. Recent evidence suggests the involvement of oxidative stress and inflammatory cytokines in the pathogenesis of FM [14,19,20]. The nociceptive aspects of FM have also been discussed in various investigations [21,22].

Connecting the physiologic & metabolic functions of melatonin with the pathogenesis & clinical manifestations of FM proposes an underlying role for melatonin in the etiopathology of FM. Recently, it was discovered that mitochondria are a potent melatonin producer [23]. Since muscles contain a large number of mitochondria, mitochondrial dysfunction could result in low melatonin production that may have some associations with fibromyalgia [24]. In support of this role, the

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study of Pernambuco et al. revealed a significantly lower levels of 6-sulphatoxymelatonin, as the main metabolite of melatonin, in the urine of FM patients in comparison with healthy controls [25]. Consequently, the melatonin effect for the treatment of FM was examined in some investigations. Yet, there is no consensus regarding the potential and the effect size of melatonin in the treatment of FM symptoms.

In this study, we aim to perform a systematic review of the clinical trials, either controlled or uncontrolled, that evaluated the effect of melatonin in the treatment of FM symptoms, including disease impact, pain, tender point count, sleep quality, fatigue, anxiety, and depression. To the best of our knowledge, no systematic review has been earlier performed on this subject.

2. Methods

2.1. Protocol and registration

This systematic review was designed based on the guidelines of the PRISMA statement [26]. The objectives, methods of the analysis, and inclusion criteria of this study were specified in advance, and the protocol was documented in www.crd.york.ac.uk/PROSPERO/under the code of CRD42018096903.

2.2. Eligibility criteria

Interventional studies, either controlled or uncontrolled and randomized or non-randomized, evaluating the efficacy of melatonin in the treatment of fibromyalgia were included. The inclusion criteria were: 1) interventional studies (controlled or uncontrolled) on the effect of melatonin in the treatment of FM; 2) conducted in adult humans; 3) studies in which melatonin treatment was the only therapeutic intervention; 4) studies with quantitative data. The exclusion criteria were: 1) studies without the outcome of interest; 2) studies in a language other than English; 3) and studies that their full-text was not available. The study was not restricted by the gender or the age of the patients.

2.3. Information sources

Database including PubMed, EMBASE, Scopus, Web of Science, and the Cochrane Library were searched without time limitation for English-language reports concerning the evaluation of the effect of melatonin in the treatment of FM. References of published original articles and reviews were searched as well.

2.4. Search

Melatonin,N-acetyl-5-methoxy tryptamine, and fibromyalgia were used as MeSH terms as follows: [(fibromyalgia) and ((melatonin) OR N-acetyl-5-methoxy tryptamine)].

2.5. Study selection and data extraction

Two investigators (A.M and A.A.K) reviewed titles and abstracts of all identified studies to decide whether the studies are eligible for this systematic review or not. Data were extracted from the eligible papers, including domains of study characteristics such as the first author's name, study location, year of publication, the sample size in each group, population, details of melatonin administration, dosage, and duration. The data extraction form was independently completed by two reviewers (A.M and F.S) and checked for discrepancies. If present, the discrepancies were resolved through discussion to achieve a consensus.

2.6. Criteria for considering studies

Types of participants: The study participants were not limited by age, gender, and disease impact so that patients with any gender, age, and disease impact were included.

Types of interventions: Clinical trials that exclusively evaluated the effect of melatonin on the treatment of FM patients were included. In studies that melatonin effect was evaluated both alone and adjunct to other FM drugs, only the melatonin alone group were included.

Types of Comparator/control: The studies were not limited by the absence or presence of comparator/control, and all interventional studies, either controlled or uncontrolled, were included. The type of control could be a placebo or no treatment group, but not other usual treatments.

2.7. Types of outcome measures

Primary outcome: Primary outcome measures were the effect of melatonin on the disease impact, pain, sleep quality, tender point count, fatigue, anxiety, stiffness, and depression of FM patients.

Secondary outcome: The 6-sulfatoxymelatonin (aMT6-s) level, as the main urinary metabolite of melatonin, was considered as the secondary outcome measure.

2.8. Risk of bias in studies

The quality of included studies and risk of bias was evaluated by Cochrane Risk of Bias Tool (RevMan 5.3.3software) that assesses the quality of study in six categories including 1) random sequence generation (selection bias); 2) allocation concealment (selection bias); 3) blinding of participants and personnel (performance bias); 4) blinding of outcome assessment (detection bias); 5) incomplete outcome data (attrition bias); and 6) other bias [27]. Accordingly, the quality was judged into three categories of "high", "low" and "unclear" risk of bias.

3. Results

Out of 224 screened studies, four studies were identified as eligible to include in this review. The flowchart of the study is demonstrated in Fig. 1. The study design was open [28] in one study and placebo-controlled trial in the others [29–31]. In two of the placebo-controlled trials, the effect of melatonin alone was compared with melatonin as an adjunct to other therapeutic agents such as fluoxetine [31] and amitriptyline [29]. Accordingly, there was no

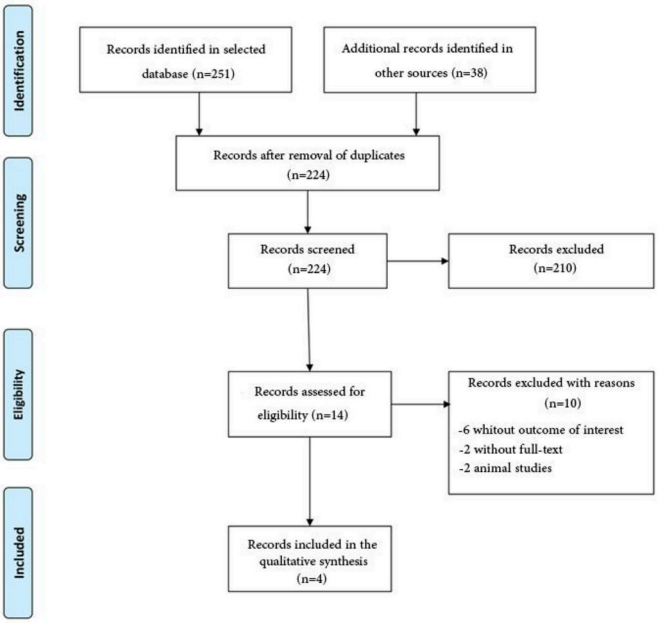

Fig. 1. Flow diagram of the study selection procedure.

placebo group to control the effect of melatonin alone in these studies. Therefore, the effect of treatment in melatonin only group (before-after) was included in this review. The other placebo-controlled trial was a longitudinal study with the administration of five different melatonin dose (3, 6, 9, 12, 15 mg) in periods of 10 days each, separated by washout periods (10 days each) [30]. The demographic characteristics of the included studies are demonstrated in Table 1.

3.1. The effect of melatonin on the evaluated outcome measures

The majority of outcome measures were evaluated in three out of four studies [28,29,31]. The study of Castaño et al. only evaluated the effect of melatonin on sleep quality and aMT6-s [30]. The types of outcome measures evaluated in each study are demonstrated in Table 2.

3.2. The effect of melatonin on the FM impact

The effect of melatonin on the FM impact was evaluated in three studies [28,29,31]. The patient and physician global assessments were used for the assessment of disease impact in the study of Citera et al. [28]. Fibromyalgia Impact Questionnaire (FIQ) was used for the evaluation of the disease impact in the study of Hussain et al. [31] and de Zanette et al. [29]. Citera et al. found a significant improvement in the mean patient and physician global assessments score after 28 days of treatment of 19 FM patients with 3 mg melatonin at bedtime [28]. Hussain et al. observed a significant reduction in both total and different components of FIQ score after 60 days of treatment of 27 FM patients with 5 mg melatonin at night time [31]. De Zenette et al. also detected a significant reduction in the mean FIQ score of 21 FM patients who were treated with 10 mg bedtime melatonin for 42 consecutive days.

3.3. The effect of melatonin on the FM pain

The effect of melatonin on the pain level of FM patients was evaluated in three studies [28,29,31]. Citera et al. [28] and de Zanette et al. [29] used the Visual Analog Scale (VAS) for the assessment of pain. Hussain et al. used the pain subset of FIQ as the measure of pain level. Citera et al. assessed the severity of pain at the selected points [28], while Hussain et al. and de Zanette et al. evaluated the general level of pain perceived by the patients [29,31]. All three studies detected a significant pain reduction following the melatonin treatment of FM patients.

3.4. The effect of melatonin on the sleep quality of FM patients

Sleep quality was evaluated as the outcome of interest in all the included articles [28–31]. Citera et al. assessed sleep quality using VAS and observed a significant improvement after the melatonin administration period [28]. Hussain et al. used the rest/sleep subset of FIQ as the measure of sleep quality and reported significant improvement following the melatonin administration period [31]. De Zanette et al. used the Pittsburgh Sleep Quality Index (PSQI) for the assessment of sleep quality and revealed a significant improvement after the treatment period with melatonin [29]. Castaño et al. evaluated the sleep quality, both subjectively and objectively. The subjective assessment was done by the PSQI. Objective assessment was performed with actigraphy. Based on their report, subjective sleep quality was improved significantly after the administration of 6, 9, 12, and 15 mg melatonin, but not after 3 mg melatonin. Moreover, six out of seven objective sleep parameters were improved after the intake of 12 and 15 mg melatonin, but not after 3, 6, and 9 mg melatonin [30].

Table 2
Types of outcome measures' of interest in included studies.

ID	First author	Outcome of interest
1	G. Citera	Disease impact, Pain, Sleep quality, Depression, Tender Point count, Fatigue, Anxiety
2	S.AR. Hussain	Disease impact, Pain, Sleep quality, Stiffness, Depression, Fatigue, Anxiety
3	S.A. de Zanette	Disease impact, Pain, Sleep quality, depression (serum BDNF), Tender Point count
4	M.Y. Castañoa	Sleep quality (objective and subjective), aMT6-s

aMT6-s: 6-sulfatoxymelatonin; BDNF: brain-derived neurotrophic factor

3.5. The effect of melatonin on the tender point count

The effect of melatonin on the tender point count of FM patients was evaluated in the studies of Citera et al. [28] and de Zanette et al. [29]. In both studies, the number of tender point count significantly reduced after the melatonin administration.

3.6. The effect of melatonin on the depression level of FM patients

The effect of melatonin on the depression level of FM patients was assessed in three out of four studies [28,29,31]. Citera et al. used VAS for the evaluation of depression. They did not find any significant effect of melatonin on the depression level of FM patients [28]. Hussain et al. used the depression subset of FIQ for the evaluation of the melatonin effect on FM depression and found a significant improvement after the treatment [31]. De Zanette et al. evaluated the effect of melatonin on the depression level of FM patients objectively by the assessment of serum brain-derived neurotrophic factor (BDNF). They observed a significant reduction in the serum BNDF following the melatonin intake [29].

3.7. The effect of melatonin on the fatigue level of FM patients

The effect of melatonin on the fatigue level of FM patients was evaluated in the studies of Citera et al. and Hussain et al. [28,31]. VAS and fatigue subset of FIQ were used for the evaluation of fatigue, respectively. Citera et al. did not find a significant improvement in the fatigue level of patients following the melatonin administration [28], but the Hussain et al. did [31].

Table 1
Demographic characteristics of the included studies.

ID	First author	Year of publication	Place of work	Design of study	Included patients	Evaluated patients	Mean age of patients (year)	Dose of melatonin (mg)	Duration of treatment (day)
1	G. Citera	2000	Argentina	Before and after	21	19	51	3	28
2	S.AR. Hussain	2010	Iraq	Placebo-controlled	27	27	38.8	5	60
3	S.A. Zanette	2014	Brazil	Placebo-controlled	21	19	47.4	10	42
4	M.Y. Castañoa	2018	Spain	Placebo-controlled	36	33	>40	3, 6, 9, 12, 15	10

3.8. The effect of melatonin on the anxiety level of FM patients

The effect of melatonin on the anxiety level of FM patients was also assessed in the studies of Citera et al. [28] and Hussain et al. [31] using VAS and anxiety subset of FIQ, respectively. A significant improvement in anxiety level was not seen in any of these studies.

3.9. The effect of melatonin on the stiffness level of FM patients

The effect of melatonin on the stiffness level of FM patients was only assessed in the study of Hussain et al. using the stiffness subset of FIQ. A significant improvement in the level of stiffness was reported after the melatonin treatment [31].

3.10. The effect of melatonin on the aMT6-s urine level of FM patients

The effect of melatonin on the urine level of aMT6-s was evaluated in the study Castañoa et al. by enzyme-linked immunosorbent assay [30]. Compared to the placebo or washing period, significantly higher levels of aMT6-s was found in the first-void morning urines of FM patients following the administration of all melatonin concentrations, including 3, 6, 9, 12, and 15 mg/day.

3.11. Risk of bias report

Selection bias was present in two out of four studies [28,30]. Performance and detection bias was present in one study [28] and unclear in the other one [30]. Attrition bias was not detected in any of the investigations. Reporting bias was detected in one study [12]. Other biases were also detected in all of the studies. The detailed and overall risk of bias based on the authors' judgments is presented in Figs. 2 and 3, respectively.

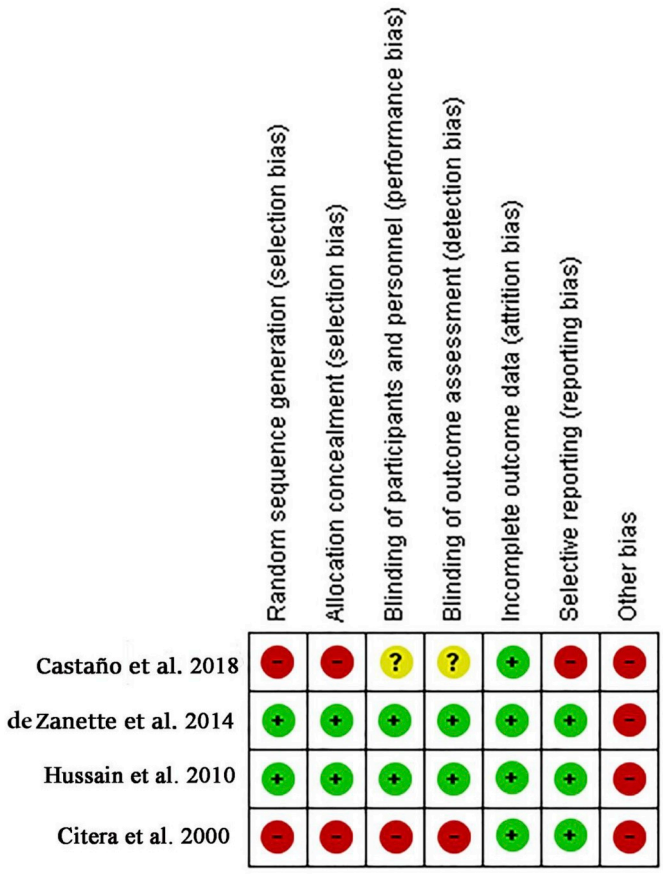

Fig. 2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

4. Discussion

In this study, we reviewed the interventional studies reporting the effect of melatonin on the treatment of FM patients. All the four studies included in this review reported the positive effect of melatonin on the improvement of FM symptoms. There was an agreement between the studies regarding the effect of melatonin on the disease impact, sleep quality, pain level, and tender point count, so that all these outcome measures significantly improved after melatonin administration. However, the results were not consistent regarding the effect of melatonin on the anxiety, fatigue, and depression level of FM patients, as some studies reported a significant effect, and some did not. The effect of melatonin treatment on the stiffness and aMT6-s level of FM patients was only evaluated in one study, which revealed a significant improvement in stiffness and a remarkable increase in urine aMT6-s level following the melatonin administration.

The study of Citera et al. was the first quantitative study that reported the effect of melatonin treatment in 21 FM patients and was published in 2000 as a pilot study with no control group. They included FM patients with symptom duration of at least six months. They excluded patients who were taking medications interfering with the melatonin level and could not be discontinued at least one week before the start of the project. After a week washing period, each patient was given a 3 mg oral melatonin 30 min before the sleep for four weeks. The mean age of the patient was 51 years, ranging from 21 to 68 years. The mean duration of disease was 24 months, ranging from 6 to 76 months. Nineteen patients completed the study. The patients and physician global assessment, tender point count and severity of pain at selected points, and sleep quality of patients were significantly improved after melatonin administration. Other outcome measures, including pain, fatigue, depression, and anxiety, were improved as well, although their improvement was not significant. Transient adverse effects, including heartburn, tremor, anxiety, and somnolence, were reported by four patients. They underlined the open design of the study as a confounding factor and suggested the evaluation of efficacy and tolerability of melatonin in FM patients in randomized double-blind trials [28].

The study of Hussain et al. was the second quantitative study that reported the effect of melatonin treatment in FM patients and was published in 2011 as a double-blind, placebo-controlled trial. This study evaluated the impact of melatonin alone or in combination with fluoxetine. Although this study was introduced as a placebo-controlled trial, no placebo only arm was included, and the comparison was only made between melatonin only and melatonin + fluoxetine group, as well as before and after treatment. The patients were randomly allocated into four study groups, including group A (20 mg/day fluoxetine + placebo, 24 patients), group B (5 mg/day melatonin + placebo, 27 patients), group C (20 mg/day fluoxetine + 5 mg/day melatonin, 27 patients) and group D (20 mg/day fluoxetine + 5 mg/day melatonin, 23 patients). Fluoxetine was administered in the morning, and melatonin was administered at night for 60 consecutive days. The mean age of the patients was 38.8 years. The improvement of FIQ score was 21.5%, 18.9%, 28.8%, and 28.9% in groups A, B, C, and D, respectively. FIQ improvement was more significant in fluoxetine + melatonin groups. However, the dose of melatonin as an adjunct to the fluoxetine had no significant effect on the FIQ improvement. In the fluoxetine-only group, all outcome measures but fatigue, sleep, and anxiety score were significantly improved. In the melatonin only group, all the outcome measures except anxiety were significantly improved. In groups C and D, all the outcome measures were significantly improved. The results were similar in groups C and D [31].

The study of de Zanette et al. was the third quantitative study that reported the significance of melatonin treatment in FM patients and was published as a phase II, randomized, double-dummy, controlled trial in

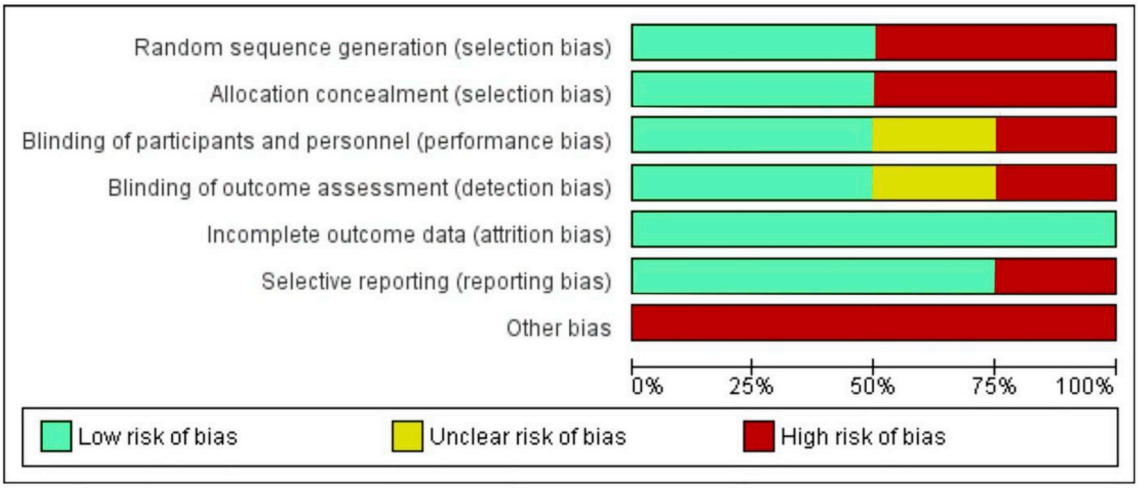

Fig. 3. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

2014. Similar to the study of Hussain et al., this study compared the impact of melatonin alone with melatonin as an adjunct. Sixty-six patients were randomly allocated into four study groups, including: 25 mg/day amitriptyline + placebo, 10 mg/day melatonin + placebo, and 10 mg/day melatonin +25 mg/day amitriptyline. Each group was comprised of 21 patients who received the allocated treatment at bedtime for six weeks. No placebo only group was included in this study. Only patients who were refractory to their current treatment were included. Patients were considered eligible if they had at least 50 mm on the 0–100 mm VAS score. Moreover, patients were allowed to remain on their analgesic medications. FIQ score, pain level, sleep quality, depression, and the number of tender points were improved significantly in all groups. The level of improvement was more in the combined group than the melatonin or amitriptyline alone groups. They pointed out the external validity issue as the main limitation of their study [29]. Allowing the patients to remain on their analgesic medication could be regarded as the other limitation of this study.

The study of Castaño et al. is the fourth and last quantitative study that reported the significance of melatonin treatment in 33 FM patients. This study was performed in 2018 with a longitudinal placebo-controlled design including five 10-day melatonin treatment periods, separated by four 10-day washout periods. Melatonin doses of 3, 6, 9, 12, and 15 mg were administered at melatonin periods, consecutively. All doses were taken 30 min before sleep for ten days. During the washout periods, the placebo was substituted with melatonin. The objective and subjective assessment of sleep quality was the primary outcome measure of interest. The mean age of the patients was not reported in this study. Regarding the objective sleep quality assessment, the intake of 6, 12, and 15 mg/day melatonin significantly reduced the sleep latency concerning basal and placebo conditions. The 12 and 15 mg/day melatonin also significantly improved sleep efficiency, immobility, actual sleep time, and assume sleep. Doses of 6, 9, 12, and 15 mg/day of melatonin significantly improved subjective sleep quality. In this respect, the dose of 12 mg/day of melatonin revealed the most significant reduction. They suggested melatonin as an adjunct therapy for the management of FM [30].

A review of the literature reveals a considerable heterogeneity between the available studies on the role of melatonin in the treatment of FM patients. This heterogeneity is seen in a variety of aspects, particularly in the design of the study. In the majority of included studies (three out of four), no placebo group was available to evaluate the effect of melatonin in comparison with no treatment group. The only controlled investigation was the study of Castaño et al. that used placebo-washout control in a cross-over design [30]. Therefore, more placebo-controlled trials are required to reach a consensus regarding the impact of melatonin in FM patients.

A remarkable discrepancy was also observed between the dosages of melatonin in different studies, ranging from 3 mg/day to 15 mg/day. Interestingly, while the dose of 3 mg/day of melatonin was reported to be efficacious in the treatment of FM symptoms in the study of Citera et al. [28], it showed no significant effect on the study of Castaño et al. [30]. Besides, the duration of melatonin administration was considerably heterogeneous, ranging from 10 to 60 days. Ferracioli-Oda et al. in a meta-analysis, reviewed the impact of melatonin in the treatment of primary sleep disorders. Based on their results, longer duration and higher doses of melatonin administration revealed more significant effects on decreasing sleep latency as well as increasing total sleep time [32]. However, the systematic review of Vural et al. on the optimal dosages for melatonin therapy in older adults suggested the lowest possible dose of immediate-release melatonin to best mimic the normal physiological circadian rhythm and to prevent prolonged supra-physiological circulating levels [33]. Hence, the optimized duration and dosage of melatonin administration in FM patients remain to be identified.

The demographic and clinical characteristics of patients in the included studies were also not comparable. Although nearly all the included patients were females, the age range of the patients was wide, so that FM patients with age ranging from 18 to 65 years were included. While in the majority of studies, a considerable number of patients were below the age of 40 years, Castaño et al. only included patients with the age of over 40 years. This difference could also be regarded as a source of heterogeneity, as melatonin levels gradually decline over the life-span, and older patients may require a higher dosage [34,35]. Castaño et al. only included patients with a total FIQ score of >70. The fibromyalgia impact was not considered in the other three investigations. However, the impact of the disease is acknowledged as a factor in determining the dosage of melatonin [35,36].

Although the results of all four quantitative studies revealed the beneficial effects of melatonin administration in the treatment of FM symptoms, the present review demonstrates a substantial heterogeneity in the variety of aspects of the studies such as study design, inclusion and exclusion criteria, dosage and duration of melatonin administration, and patients' characteristics. Even so, melatonin could still be regarded as a valuable treatment of choice in FM patients, as the other available pharmacological treatment of fibromyalgia are associated with a variety of adverse effect and limited benefits. For example, duloxetine, as one of the main pharmacological treatment in FM patients, is associated with a high rate of discontinuation and adverse events including dry mouth, vomiting, decreased appetite, constipation, insomnia, dizziness, fatigue, somnolence [37,38].

The present systematic review was not without weakness. The main limitation of this study was the very limited number of studies that did not allow performing a meta-analysis. Besides, Gray literature was not searched in this review due to a lack of access. Considering the significant amount of heterogeneity between the available studies, the current review urges the need to perform more high-quality controlled clinical trials on the effect of melatonin in FM patients.

5. Conclusion

Melatonin treatment has several positive effects on FM patients, including the improvement of sleep quality, pain, and disease impact. By contrast to conventional pharmacological agents such as duloxetine, no major adverse events were reported following the melatonin consumption. Therefore, melatonin could be regarded as a safe and efficacious treatment in FM. Nevertheless, the significant level of heterogeneity between the available studies urges the need to perform further high-quality investigations in this respect.

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Declaration of competing interest

The authors declare no competing interest to disclose.

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